



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

Applicant: Henslee et al.

Serial No.: 09/975,502

Filed: October 11, 2001

For: REAGENTS AND METHODS USEFUL
FOR DETECTING DISEASES OF THE
BREAST

Case No.: 5972.US.P7

Examiner: Harris, A.

Group Art Unit: 1643

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DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Barry Dowell, do hereby declare and state that:

I am a citizen of the United States of America and
reside at 197 Knightsbridge Drive, Mundelein, Illinois
60060.

I graduated in 1972 from the University of North
Carolina at Chapel Hill and received a B.S. degree in
Zoology, and I graduated in 1977 from the University of
Tennessee Center for the Health sciences and received a
Ph.D. degree in Microbiology and Immunology (see the
attached curriculum vitae).

I have been employed as a Manager, Cancer Core R&D, Abbott Diagnostics Division at Abbott Laboratories, Abbott Park, Illinois since 2004. I have been employed in several other positions at Abbott Laboratories since 1987.

I have read and am familiar with the specification and pending claims of U.S. Patent Application Serial No. 09/975,502. Furthermore, I have reviewed the Office Action of November 1, 2005 issued by the Examiner in the above-referenced application and have reviewed the prior art cited by the Examiner with respect to the obviousness rejection of claims 2-4.

In my opinion, one of ordinary skill in the art would not have been motivated to have created the subject matter of claims 2-4, at the time of filing of the application, based upon the teaching of U.S. Patent Application Publication No. 2002/0009738A1 (Houghton et al).

Houghton et al. describe the identification of tissue-specific polynucleotides and methods for determining the presence of cancer in a patient by detecting polynucleotides which encode breast tumor proteins.

The Examiner contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use antibodies via an immunoassay in the detection of the taught breast tumor proteins in a patient sample within a tissue section or cell culture, and that one would have been motivated to do so with a reasonable expectation of success by the

teachings of Houghton et al. to detect two breast tumor proteins. In particular, the Examiner notes that the publication discloses that "what is needed in the art is a methodology that employs the detection of two or more breast cancer specific genes in order to improve the sensitivity and reliability of detection of micrometastases". (Page 1, section 0009.) Thus, the Examiner concludes that it would follow that detection of encoded polypeptides would be useful in the diagnosis of breast cancer.

In my opinion, the Examiner is incorrect with respect to the conclusions made. It is certainly not obvious that because a gene is expressed, the encoded protein is automatically expressed as well as secreted. In fact, Houghton et al. do not even disclose expressed proteins whatsoever. It must be emphasized that all expressed polynucleotides do not result in increased expression of the respective encoded polypeptides for various reasons; thus, it would not have been obvious that measuring the polypeptide of interest would be useful from a diagnostic perspective. Further, the presence of two polynucleotides, for example, would not have rendered obvious, or motivated one of ordinary skill in the art, to predict the presence of the two encoded proteins of a specific combination. Moreover, the use of the separate antibodies to separately find each member of the combinations of specific polypeptides is certainly not obvious.

In view of the above, one of ordinary skill in this field would not have been motivated to have created the

Declaration of Dr. B. Dowell
U.S. Patent Appln. No. 09/975,502

subject matter of claims 2-4 based upon the teachings and suggestions of Houghton et al. Significant skill was required in connection with the subject matter of claims 2-4 of the above-referenced application.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Respectfully submitted,

By: Barry Dowell
Dr. Barry Dowell

Date: 12/15/05



RESUME

Barry Lee Dowell, Ph. D.

CURRENT POSITION

Associate Research Fellow, Volwiler Society
Manager, Cancer Core R&D

EDUCATION

- 1972 B. S. (Zoology), University of North Carolina at Chapel Hill
1977 Ph. D. (Microbiology and Immunology), University of Tennessee Center for the Health Sciences, Memphis
1977-1979 Postdoctoral Fellow (NRSA), Department of Microbiology and Immunology, Duke University, Durham, North Carolina

PROFESSIONAL ORGANIZATIONS

American Association for the Advancement of Science
American Association of Clinical Chemists
American Association of Immunologists
American Society for Microbiology
Clinical Ligand Assay Society

HONORS AND AWARDS

- 1980-1982 Special Fellow, Leukemia Society of America
1983-1984 Biomedical Research Support Grant
1985 Geometric Cell Labelling Grant
1986-1987 Ronald McDonald Children's Charities Grant
1989 Chairman's Award, Abbott Laboratories, IMx APF
1991 Chairman's Award, Abbott Laboratories, IMx PSA
1992 Abbott Diagnostics Division Technical Advisory Board, Entrepreneurial Award for IMx PSA Team
1992-Present Associate Research Fellow, Volwiler Society
1993, 1994 Member and Presenter for First and Second Stanford Conference for the International Standardization of PSA
1993-1996 Full Member, PSA Standardization Subcommittee of National Committee for Clinical Laboratory Standards
1997 Abbott Diagnostics Division Technical Advisory Board, Technology Award for Free PSA Team
1997 Chairman's Award, AxSYM Free and Total PSA
1997 Member, Steering Committee, ISOBM TD-3 (PSA Antibody) Workshop
1998 Expert Reviewer for Urology
2000-2001 Two VP Awards for FDA Compliance Efforts (Conjugate Common Process)
2003-2004 Member of NACB Committee for Guidelines for Prostate Cancer Diagnosis

PROFESSIONAL EMPLOYMENT

1972-1978	Microbiology Teaching Assistant, Department of Microbiology, University of Tennessee Center for Health Sciences, Memphis
1980-1981	Research Associate, Department of Microbiology and Immunology, Duke University, Durham, North Carolina
1981-1982	Medical Research Associate, Cancer Center Faculty, Department of Microbiology and Immunology, Duke University, Durham, North Carolina
1982-1987	Assistant Professor, Departments of Pediatrics and Microbiology and Immunology, Baylor College of Medicine, Houston, Texas
1987-1989	Project Manager for IMx APF, Biologist II, Cancer Product Development, Research and Development, Abbott Laboratories, Abbott Park, Illinois
1989-1991	Project Manager for IMx PSA, Senior Research Biochemist, Cancer Product Development, Research and Development, Abbott Laboratories, Abbott Park, Illinois
1991-1992	Group Leader for IMx CA15-3, IMx PAP, PSA Futures, Research Invest. Biochemist, Cancer Product Development, Research and Development, Abbott Laboratories, Abbott Park, Illinois
1992-1994	Group Leader for IMx CA15-3, IMx PAP, PSA Futures, Cancer Product Research and Development and Associate Research Fellow, Volwiler Society Abbott Laboratories, Abbott Park, Illinois
1995-1996	Lead Scientist for AxSYM Total PSA and AxSYM Free PSA, Cancer Product Research and Development and Associate Research Fellow, Volwiler Society Abbott Laboratories, Abbott Park, Illinois
1996-1998	Project Manager for AxSYM Total PSA and AxSYM Free PSA, Cancer Product Research and Development and Associate Research Fellow, Volwiler Society Abbott Laboratories, Abbott Park, Illinois June, 1996
1998-1999	R&D Manager, Diseases of Aging Venture Group and Associate Research Fellow, Volwiler Society Abbott Laboratories, Abbott Park, Illinois
1999-2000	R&D Manager, Breast Cancer Venture Group and Associate Research Fellow, Volwiler Society Abbott Laboratories, Abbott Park, Illinois
2000-2001	Manager of Conjugation Common Process and Associate Research Fellow, Volwiler Society Abbott Laboratories, Abbott Park, Illinois
2001-2004	Manager, Cancer Core R&D and Associate Research Fellow, Volwiler Society Abbott Laboratories, Abbott Park, Illinois
2004-Present	Manager, Cancer Core R&D and Research Fellow, Volwiler Society Abbott Laboratories, Abbott Park, Illinois

PATENT APPLICATIONS AND SUPPORT

1. Provided scientific support for licensed technology patents from Wallac, OY, Turku, Finland on Assay of Free and Complexed Prostate-Specific Antigen, including technical support for successful defense of European Patent Opposition in Munich, March, 2003.
2. Dowell, B., King, C., Smith, A., and O'Morchoe, S. Immunoassys for Prostate Specific Antigen. Issued February, 1997. Patent describes use of monoclonal antibody additive to monoclonal-polyclonal PSA assays to improve ability to detect free PSA and PSA-ACT complexes equally. WO 9518381 and US 5559677 This method is currently being used in Architect Total PSA assay.
3. Dowell, B., King, C., Smith, A., and O'Morchoe, S. Immunoassys for Prostate Specific Antigen. Issued September 30, 1997. Patent describes use of PSA-Free PSA antibody as a calibrator that mimics PSA-ACT. It also describes method of fractionating polyclonal antibodies into epitopes that are masked by binding to PSA-ACT. US 5672480
3. Bridon, D., Dowell, B., Qiu, X, Petterson, K., Piiroinen, T., Lilja, H. and Vihinen, M. Prostate Specific Peptides and Uses Thereof. US 6,143,509.

REGULATORY SUBMISSION SUPPORT

1. Member of PMA Submission Team for IMx AFP, which was first PMA supplement on IMx instrument. Efforts included presentation of IMx Instrument to FDA in Bethesda.
2. Member of 510K Submission Team for IMx PAP.
3. Member of PMA Submission Team for IMx PSA, which was first full PMA for cancer product on IMx. Efforts included presentation of performance characteristics and rare reagent characterization at FDA Panel Meeting.
4. Member of PMA Submission Team for AxSYM Free and Total PSA.
4. Supported French and Koseisho submissions for IMx AFP, IMx PAP, IMx CA15-3, AxSYM Free PSA, and AxSYM Total PSA.
5. Independent Reviewer for IMx Free and Total PMA submitted January 30, 2003 and approved in 2004.

TEST METHOD AND PROCESS VALIDATION SUPPORT

1. Project manager for AxSYM Free and Total PSA assays which were among first AxSYM assays to be fully validated, including primaries, rare reagents and list components under then current guidelines.
2. Manager for Conjugate Common Process, which covered PVA's for AP and HRPO periodate and forward and reverse heterobifunctional conjugation. Also covered test method for acridinium incorporation ratio and for % conjugation by GPC-HPLC.

ABBOTT COMMITTEES

1. ADD Cancer New Leads Assessment Committee, Manager
2. ADD Assay Standardization Committee

ABBOTT PUBLICATIONS

1. Perspectives on PSA. Abbott Diagnostics Educational Services, Technical Brochure, 1993.
2. Dowell, B., Schaefer, V., Crary A., and Weigand, R. Performance and clinical evaluation of AxSYM Free and Total PSA. Abbott PSA Monograph, Oscar Securado Editor., Abbott Diagnsotics Educational Services (Delkenheim), 1997, pages 9-13.

SELECTED ABBOTT SPONSORED PRESENTATIONS

1. Tumor Markers: An Overview. Oklahoma-Arkansas Bi-State Medical Technology Convention, Oklahoma City, OK, April 25, 1990.
2. Clinical Use and Development of Cancer Markers. William Beaumont Hospital Clinical Pathology Inservice, Royal Oak, MI. November 2, 1990.
3. Description and Utility of Available Tumor Markers. New Mexico State Society of American Medical Technologists 1991 Fall Meeting, Albuquerque, NM. September 28, 1991
4. The Biochemistry of PSA: A Complex Problem. Annual Scientific Symposium of Ontario Society of Clinical Chemists. North York, Ontario. November 3, 1993.
5. Cancer BU Experience with *E. coli* Alkaline Phosphatase (Discrepant Avoidance). ADD Technical Advisory Board Roundtable on Alkaline Phosphatase. Novmber 4, 1994.
6. PSA: Characteristics and Immunodetection. Annual Meeting of Private Laboratory Owners. San Juan, Puerto Rico, May 28, 1994.
7. Performance and Clinical Characteristics of Free and Total PSA. Clinical Investigators Meeting: Free PSA. European Urological Association, Paris, August, 1996.
8. Roundtable for Clinical Ligand Assay Society Annual Meeting. Use of Free PSA in Diagnosis of Prostate Cancer. March 24, 1997, Chicago, IL.
9. Abbott Day. Characteristics of AxSYM Free and Total PSA assays., Linx Austria, June 10, 1997,
10. Abbott Days. Utility of Free PSA and Characteristics of AxSYM Free and Total PSA assays. Maidenhead, England. June 18 and 19, 1997.
11. Member of Industry Roundtable for AACC Tumor Markers in Prostate Cancer Workshop, Chicago 2001, 2002 and 2003
12. Conjugation Common Process. For R&D, Operations and Quality, September, 2001.
13. Industry Rountable for Annual Meeting of Clinical Ligand Assay Society, Chicago, IL, May 2004. Guidelines for colorectal cancer screening
14. Tumor Marker Workshoop for Annual Meeting of Clinical Ligand Assay Society, Chicago, IL, May 2004.

BIBLIOGRAPHY

PUBLICATIONS

1. Dowell, B. L.: Properties of *in vitro* cultured Hodgkin's disease cells. Dissertation, June, 1977.
2. Robert, A. N., Smith, K. C., Dowell, B. L., and Hubbard, A. K.: Cultural, morphological, cell membrane, enzymatic and neoplastic properties of cell lines derived from a Hodgkin's disease lymph node. *Cancer Res.* 38: 3033-3043, 1978.
3. Dowell, B. L., Falletta, J. M., Moore, J. O., and Metzgar, R. S.: Detection and partial characterization of human thymus-leukemia antigens. *J. Nat. Cancer Inst.* 65:691-701, 1980.
4. Dowell, B. L., Segars, J. H., and Metzgar, R. S.: Physical separation of adenosine deaminase and a human thymus-leukemia antigen isolated from Molt 4. *Cancer Res.* 41:343-345, 1981.
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7. Vogler, L. B., Crist, W., Sarraf, A., Pullen, J., Bartolucci, A., Falletta, J., Dowell, B., Humphrey, B. G., Blackstock, R., van Eys, J., Metzgar, R. S., and Cooper, M. D.: An analysis of clinical and laboratory features of acute lymphocytic leukemias with emphasis on 35 children with pre-B leukemia. *Blood* 58:135-140, 1981.
8. Metzgar, R. S., Borowitz, M., Jones, N. H., and Dowell, B. L.: The distribution of common ALL antigen (CALLA) in non-hematopoietic tissues. *J. Exp. Med.* 154:1249-1254, 1981.
9. Haynes, B. F., Dowell, B. L., Hensley, L. L., Gore, I., and Metzgar, R. S.: Reactivity of T cell monoclonal antibodies with primate lymphocytes. *Science* 215:298-300, 1982.
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13. Dowell, B. L., Tuck, F. L., Borowitz, M. J., LeBien, T. W., and Metzgar, R. S.: Phylogenetic distribution of a 24,000 dalton human leukemia-associated antigen on platelets and kidney cells. Comparative and Develop. Immunol. 8:187-195, 1984.
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15. Borowitz, M. J., Dowell, B. L., Boyett, J. M., Falletta, J. M., Pullen, J., Crist, W. M., Humphrey, G. B., and Metzgar, R. S.: Monoclonal antibody definition of T-cell acute leukemia. A Pediatric Oncology Group Study. Blood 65:785-788, 1985.
16. Crist, W., Pullen, J., Boyett, J., Falletta, J., van Eys, J., Borowitz, M., Jackson, J., Dowell, B., Frankel, L., Quddus, F., Ragab, A., and Vietti, T.: Clinical and biologic features predict poor prognosis in acute lymphoid leukemias in infants: A Pediatric Oncology Group study. Blood 67:135-140, 1986.
17. Borowitz, M. J., Dowell, B. L., Boyett, J. M., Pullen, D. J., Crist, W. M., Quddus, F. M., Falletta, J. M., and Metzgar, R. S.: Clinicopathologic aspects of E rosette negative T cell acute lymphoblastic leukemia. A Pediatric Oncology Group study. J. Clin. Oncol. 4:170-177, 1986.
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37. Leinonen, J., Leinimaa, M., Zhang, W.-M., Piironen, T., Pettersson, K., Lilja, H., Dowell, B., and Stenman, U-H. Reactivity of anti-PSA monoclonal antibodies with recombinant human kallikrein-2. *Tumor Biol.* 20 (Suppl. 1):35-37, 1999.
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ABSTRACTS

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2. Dowell, B. L., Roberts, A. N., and Smith, K. L.: Properties of *in vitro* cultured Hodgkin's disease cells. Bacteriol. Proc. 76:66, 1976.
3. Dowell, B. L., and Metzgar, R. S.: Detection of a human thymus-leukemia antigen by monkey antisera to human thymocytes. Fed. Proc. 38:1461, 1979.
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10. Dowell, B. L., and Mukhopadhyay, N.: A possible prognostic value of mitogenic responses in non-T, non-B childhood acute lymphocytic leukemia (ALL). Proc. Southwest Section, American Association for Cancer Research, New Orleans, Louisiana, October 27-28, 1983.
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